#13

Docket No.: PF-0321-2 DIV

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Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1653

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By: _____ Printed: Lisa McDill

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Bandman et al.

Title: DISEASE ASSOCIATED PROTEIN KINASES

Serial No.:	09/769,970	Filing Date:	January 24, 2001
Examiner:	Carlson, K.C.	Group Art Unit:	1653

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed July 1, 2003, and received by the USPTO on July 3, 2003, and in consideration of the Advisory Action mailed July 15, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $ **320.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting Claims 24, 27-29, and 31 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc., (now Incyte Corporation, formerly known as Incyte Genomics, Inc.) (Reel 9010, Frame 0834) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 24, 27-29, and 31
Claims allowed:	Claims 25 and 26
Claims canceled:	Claims 1-21, and 32
Claims objected to:	Claim 30
Claims withdrawn:	Claims 22, 23, and 33-42
Claims on Appeal:	Claims 24, 27-29, and 31 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, *inter alia*, to polynucleotides encoding a polypeptide ("DAPK-2") having homology to human vaccinia virus related kinase VRK1 (GI 1827450), which have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of DAPK-2, for toxicology testing, and for drug discovery (see the Specification at, e.g., page 42, line 10 through page 47, line 9). As described in the Specification:

> DAPK-2 (SEQ ID NO:2) was first identified in Incyte Clone 40194 from the TBLYNOT01 cDNA library using a computer search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:9, was derived from the extended and overlapping nucleic acid sequences: Incyte Clones 40194/ TBLYNOT01, 278198/ TESTNOT03, and 1683885/ PROSNOT15.
>
> Therefore, in one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:2. DAPK-2 is 448 amino acids in length and has a potential ATP-binding sequence at G_{36}SGGFGLI and an STK specific signature sequence at Y_{162}VHGDVKAANLLL. As shown in Fig. 2,

DAPK-2 has sequence homology with the human vaccina virus related kinase, VRK1 (GI 1827450). In particular, DAPK-2 and VRK1 share 65% homology. DAPK-2 and VRK1 share the glycine-rich ATP-binding sequence and the STK signature sequence described above. DAPK-2 is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses. (Specification, page 18, lines 3-15.)

(6) ISSUES

1. Whether the polynucleotides of Claims 24, 27-29, and 31 meet the written description requirement of 35 U.S.C. §112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together and thus stand or fall together.

(8) APPELLANTS' ARGUMENTS

Issue 1: Rejection of Claims 24, 27-29, and 31 Under 35 U.S.C. § 112, first paragraph, written description

Claims 24, 27-29, and 31 were rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. The Examiner alleged that "[w]ithout a statement regarding the activity of a polynucleotides [*sic*] encoding a polypeptide have [*sic*] 90% identity to SEQ ID NO:2, or polynucleotides that are 90% identical to SEQ ID NO:9 and encode a polypeptide having any function one skilled in the art cannot know the metes and bounds of the claimed polynucleotides." (Final Office Action, page 3.)

The Examiner ignores the claim limitations of "having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2" and "having at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO:9," and attempts to introduce a limitation of "function" to the polypeptide variants and polynucleotide variants, limitations which are not present in the pending claims. The Examiner ignores the limitation that the claimed polynucleotides encode a polypeptide comprising a naturally occurring amino acid sequence or comprise a naturally occurring polynucleotide sequence.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (citations omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:2 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 61-62 and 68-69). Variants of SEQ ID NO:2 are described, for example, at page 16, lines 19-27. In particular, the preferred, more preferred, and most preferred SEQ ID NO:2 variants (80%, 90%, and 95% amino acid sequence identity to SEQ ID NO:2) are described, for example, at page 21, lines 2-6. Incyte clones in which the nucleic acids encoding the human DAPK-2 were first identified and libraries from which those clones were isolated are described, for example, at page 18, lines 3-7 of the Specification. Chemical and structural features of DAPK-2 are described, for example, on page 18, lines 8-14. The Specification describes (e.g., page 50, line 30 through page 51, line 25) how to use BLAST to determine whether a given sequence falls within the "having at least 90% sequence identity" scope. Given SEQ ID NO:2,

one of ordinary skill in the art would recognize "a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2." Given SEQ ID NO:9, one of ordinary skill in the art would recognize "a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO:9."

There simply is no requirement that the claims recite particular variant polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants are defined in terms of SEQ ID NO:2 ("An isolated polynucleotide encoding a polypeptide selected from the group consisting of. . . b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2." The polynucleotide variants are defined in terms of SEQ ID NO:9 ("An isolated polynucleotide selected from the group consisting of. . . b) a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO:9.")

Because the recited polypeptide variants are defined in terms of SEQ ID NO:2, and the recited polynucleotide variants are defined in terms of SEQ ID NO:2 and SEQ ID NO:9, the precise chemical structure of every polypeptide variant and every polynucleotide fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35

U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claims 24 and 31 recites chemical structure to define the claimed genus:

> 24. An isolated polynucleotide encoding a polypeptide selected from the group consisting of. . . :
>
> b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2.
>
> 31. An isolated polynucleotide selected from the group consisting of . . . :
>
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO:9 . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO: 2 and SEQ ID NO:9. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Final Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claims do not define a genus which is highly variant

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variant. Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078) (Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to disease associated protein kinases related to the amino acid sequence of SEQ ID NO:2. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as disease associated protein kinases and which have as little as 40% identity over at least 70 residues to SEQ ID NO:2. The "variant language" of the present claims recites, for example, polynucleotides encoding "a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2" (note that SEQ ID NO:2 has 448 amino acid residues). This variation is far less than that of all potential disease associated protein kinases related to SEQ ID NO:2, i.e., those disease associated protein kinases having as little as 40% identity over at least 70 residues to SEQ ID NO:2.

Furthermore, Appellants note that it is well known in the art that sequence similarity is predictive of similarity in functional activity. Hegyi and Gerstein ("Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins," Genome Research (2001) 11: 1632-1640; Reference No. 2) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Reference No. 2, page 1635.) Hegyi and Gerstein also concluded that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the

same in this case was 91%." (Reference No. 2, page 1636.) Hegyi and Gerstein (Reference No. 2, page 1632) further note that

> Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found that precise function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

The polypeptides encoded by the claimed polynucleotides share more than 90% sequence identity with the SEQ ID NO:2 polypeptide, well above the thresholds described in the Hegyi and Gerstein article (Reference No. 2) cited above. Therefore, there is a reasonable probability that the SEQ ID NO:2 polypeptide variants would have the same function as the SEQ ID NO:2 polypeptide.

And, in any case, the "function" of the claimed polynucleotides and polypeptides encoded by the claimed polynucleotides is immaterial to their use, as described in the Specification and as well known in the art, in toxicology testing (see the Specification at, e.g., page 42, line 10 through page 47, line 9).

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 19, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of

the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:2 and SEQ ID NO:9, and the additional extensive detail provided by the subject application, the present inventors were in possession of the recited polypeptide variants and polynucleotide variants at the time of filing of this application.

D. Summary

The Final Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2 or SEQ ID NO:9. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides or polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. and Hegyi and Gerstein. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Final Office Action.

(9) CONCLUSION

Appellants request that the rejections of the claims on appeal be reversed for at least the reasons above.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

Date: August 28, 2003

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Enclosures:

1. S. E. Brenner et al., Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998). (previously submitted also with the Response to Office Action filed February 3, 2003)

2. H. Hegyi and M. Gerstein, Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins, Genome Research 11: 1632-1640 (2001)

APPENDIX - CLAIMS ON APPEAL

24. (As Once Amended) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of SEQ ID NO:2, and

b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2.

27. (As Once Amended) A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 24.

28. (Reiterated) A cell transformed with a recombinant polynucleotide of claim 27.

29. (As Once Amended) A method of producing a polypeptide selected from the group consisting of a polypeptide comprising an amino acid sequence of SEQ ID NO:2 and a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:2, the method comprising:

a) culturing the cell of claim 28, and

b) recovering the polypeptide so expressed.

31. (As Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:9,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO:9,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).